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NON-HAZARDOUS SYNTHESIS OF ISOCEPHOSPORIN INTERMEDIATES VIA α-VINYLAMINO-β-LACTAMS(*1*)

Ajay K. Bose*, Maghar S. Manhas, Shanti G. Amin, Jagdish C. Kapur,
J. Kreder, L. Mukkavilli, Bhagat Ram, John E. Vincent
Department of Chemistry and Chemical Engineering, Stevens Institute of Technology
Hoboken, New Jersey 07030, U.S.A.

The reaction of a Schiff Base derived from veratrylamine and cinnamaldehyde with (α-methyl-β-alkoxycarbonyl)-vinylamino acetic acid (from glycine and an acetoacetate ester) in presence of a chloroformate ester and triethylamine constitutes a safe synthesis of α-vinylamino β-lactams that can be converted by literature methods to known intermediates for the synthesis of isocephalosporins and analogs.

The reaction of β-dicarbonyl compounds with α-amino acids and alkali leads to amino-protected amino acids or "Dane Salts"(*2*) which have been used for the preparation of peptides(*2*) and for the acylation of 6-APA to ampicillin(*3*) and 7-ADCA to cephradine(*4*). In the hope of synthesizing novel β-lactams we attempted to condense Dane salts from phenylalanine and alanine with benzalaniline in the presence of a chloroformate ester and triethylamine but failed.

We(*5*) have discovered, however, that Dane salts (1), from glycine can convert certain imino compounds to α-vinylamino-β-lactams (2). Chloroacetonitrile which has been used with Dane salts to form active esters for peptide synthesis(*2*) was not effective for β-lactam synthesis. But, we have found that chloroformate esters and phosphochloridate esters are convenient activating agents(*6*) for our synthesis.

We describe here the preparation of (2), an intermediate for isocephalosporins, as an illustration of this synthitic approach (see Scheme 1).

***cis*-1-(3', 4'-dimethoxybenzyl)-3-(α-methyl-β-carbomethoxy-vinylamino)-4-styryl-2-azetidinone(2).** N-[1-methyl-2-methoxycarbonyl-vinyl]-glycine, potassium salt (12.66 g, 60 mmole) was suspended in anhydrous methylene chloride (250 ml) to which was added triethylamine (6.06 g, 60 mmole). The reaction mixture was cooled (-20°) and ethyl chloroformate (6.51 g, 60 mmole) in anhydrous methylene chloride (20 ml) was added dropwise. After the addition was completed, the golden solution was allowed to stir at -20° for 30 min. A solution of the unpurified imine (8.22 g, 30 mmole), derived from *trans*-cinnamaldehyde and veratrylamine (6.06 g, 60 mmole) in anhydrous methylene chloride (30 ml) was then added dropwise. The solution was allowed to stir with warm

to room temperature overnight. The solution was then filtered, the filtrate washed with 5% $NaHCO_3$ (1 x 150 ml), brine (2 x 150 ml), dried (Na_2SO_4) and evaporated to yield 16.5 g of a crude oil which, upon chromatography on 300 g Davison silica gel (100-200 mesh), $CHCl_3$-EtAc (10:5) as eluent, yielded the *cis*-β-lactam 2 (6.02 g, 49.0%) as an oil. IR (neat): 2900, 1755, 1720, 1660, 1615, 1520 cm^{-1}. NMR ($CDCl_3$): δ 1.90(s, 3H), 3.70(s, 3H), 3.90(s, 3H), 4.35(dd, 1H, J=4.5, 9 Hz), 4.6(d, 2H, J=5 Hz), 4.9(dd, 1H, J=4.5, 9Hz), 6.05(dd, 1H, J=9, 16 Hz), 6.07(s, 1H), 6.85(d, 1H, J=16 Hz), 6.9(s, 3H), 7.35(s, 5H), 9.1(d, 1H, J=9 Hz). EIMS: M+/e = 436 observed.

The vinylamino β-lactam 2 was hydrolyzed (p-TSA-H_2O, dioxane, room temp.) to an α-amino-β-lactam which was acylated with phenoxyacetyl chloride in methylene chloride to yield, after chromatography, 7 (50% yield from 2). Persulfate oxidation (*8*) of the 3,4-dimethoxybenzylamine group afforded 8 in 21% yield. Permanganate oxidation in acetone-water, followed by treatment with diazomethane provided the ester 9 (*9*) in overall 27% yield from 8. The conversion of 9 to the 2-aza-3-carboxy-7-phenoxyacetamido derivative (10), an azapenicillin analog, has been described by Huffmann et al (*8*).

The α-amino-β-lactam obtained by the hydrolysis of 2 (see above) was acylated with 2-thienylacetyl chloride in methylene chloride to provide, after chromatographic purification, 3 (56% from 2). Persulfate oxidation of (3) gave an 18% yield of the N-unsubstituted β-lactam 4. Permanganate oxidation of 4 to a carboxylic acid with subsequent reaction with diazomethane furnished a 32% yield of the methyl ester 5. Sodium borohydride reduction of 5 in wet THF (0°) to the alcohol 6a was followed by tosylation (p-toluenesulfonyl chloride, pyridine, methylene chloride, 0°) to yield 6b (overall 41% from 5) (*9*). This intermediate has been converted by Bryan et al. (*10*) to the isocephalosporin 11 in good yield.

Two different routes to isocephalosporins (7-amido-2-thia-3-octems) have been reported recently (*10, 11*). The crucial β-lactam formation step in both approaches involves the reaction of the chloride (*11*) or a mixed anhydride (*10*) of azido acetic acid with an imino compound and triethylamine. Our earlier synthesis of α-amido β-lactams via α-azido β-lactams (*12*) is currently in wide use in various research laboratories for the total synthesis of β-lactam antibiotics (*13*). Since azidoacetic acid, its chloride and other derivatives are prone to explosive decomposition and are therefore unsuitable for large scale use, we have been searching for safer approaches to α-amino β-lactams (*14*). The synthesis of α-vinylamino β-lactams using "Dane Salts" from glycine constitutes a hazard-free, economical method for the stereospecific synthesis of α-amido β-lactams on a large scale (*15*).

We have also found a novel way to generate the α-amido side chain without the intermediacy of an α-amino β-lactam. If 12 is ozonated in methylene chloride solution at -78° and then oxidized with Jones reagent, an α-amido β-lactam (13) is obtained in good yield. When a cyclic β-keto ester, such as 2-cyclohexanone carboxylate, was the dicarbonyl component for protecting the amino group of glycine, ozonation under oxidative conditions led to an α-amido side chain with an α-keto ester at the end of the chain. The potential of this approach for further modification of the side chain is being explored.

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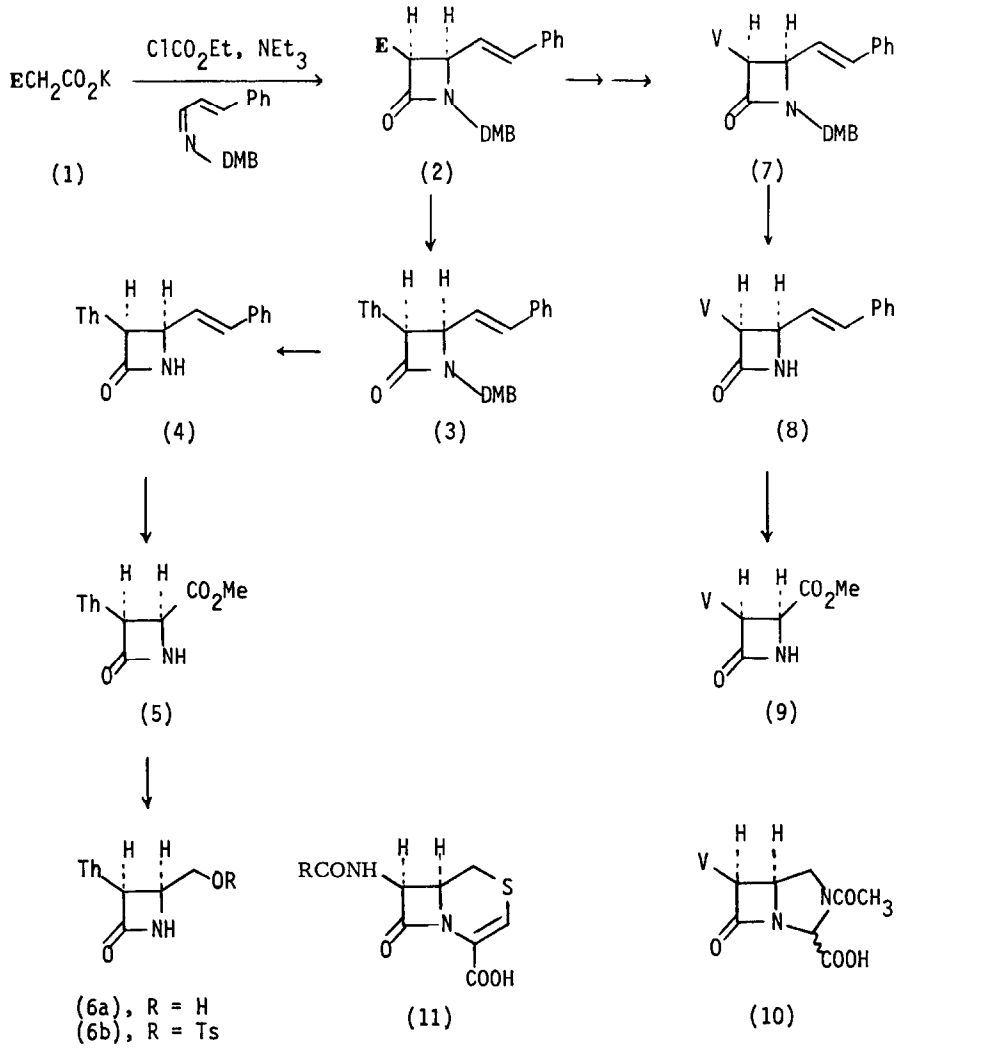
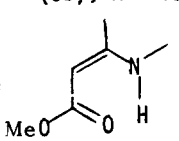
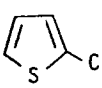
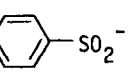
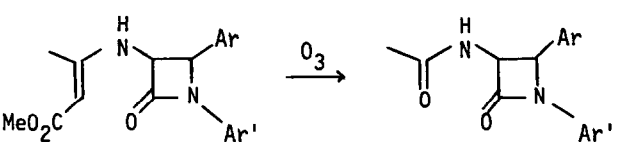
Scheme 1



E =  , V = $PhOCH_2CONH$, Th =  CH_2CONH, Ts = 

DMB = 3,4-dimethoxybenzyl



References and Notes

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5. a) A.K. Bose, M.S. Manhas, S.D. Sharma, and S.G. Amin, unpublished preliminary work done at Stevens Institute of Technology, 1971.
   b) A.K. Bose, patent application pending.
   c) Extracted in part from the following theses submitted to Stevens Institute of Technology: i) J.F. Kreder, Oxidation of Beta-Lactam Derivatives, B.S. Thesis, May, 1977.
   ii) L. Mukkavilli, Synthesis of α-Amino β-Lactams, M.S. Thesis, May, 1978.
   iii) J.E. Vincent, Total Synthesis of Isocephalosporin Analogs, Ph.D. Thesis, May, 1979.

6. While this manuscript was in preparation S.D. Sharma who was a member of our research group at the early stages of this project(5a) reported(*7*) the use of phosphorous oxychloride as the activating agent for the preparation of some α-vinylamino β-lactams. To avoid duplication, we omit from our report the description of analogous β-lactams(5c).

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9. The mp and spectral properties of this compound were identical with those reported by Bryan et al. (*10*).

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12. A.K. Bose, B. Anjaneyulu, S.K. Bhattacharya and M.S. Manhas, *Tetrahedron*, *23*, 4769 (1967).

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14. A.K. Bose, M.S. Manhas, H.P.S. Chawla, and B. Dayal, *J.C.S. Perkin I*, 1880, (1975).

15. α-Phthalimido β-lactams can be prepared safely and cleaved to α-amino β-lactams, for example, see J. Finkelstein, K.G. Holden and C.D. Perchonock, *Tetrahedron Lett.*, 1629 (1978).

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